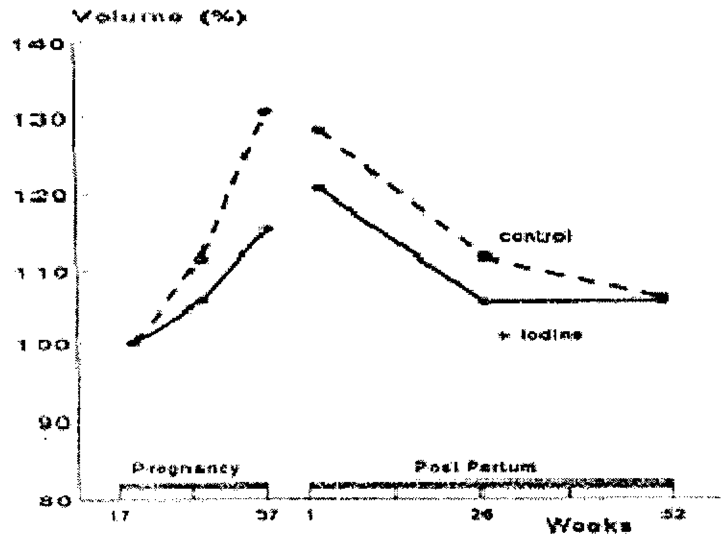

Figure 8. Median thyroid volume during pregnancy and 52 weeks postpartum in women receiving iodide supplementation and control women, as percent of initial values. In both groups, significant increases during pregnancy and decreases during the postpartum period were found ($p<0.05$). The increase during pregnancy in controls was higher than that in the iodide-supplemented group ($p<0.05$) (from Pedersen *et al.*, 1993).

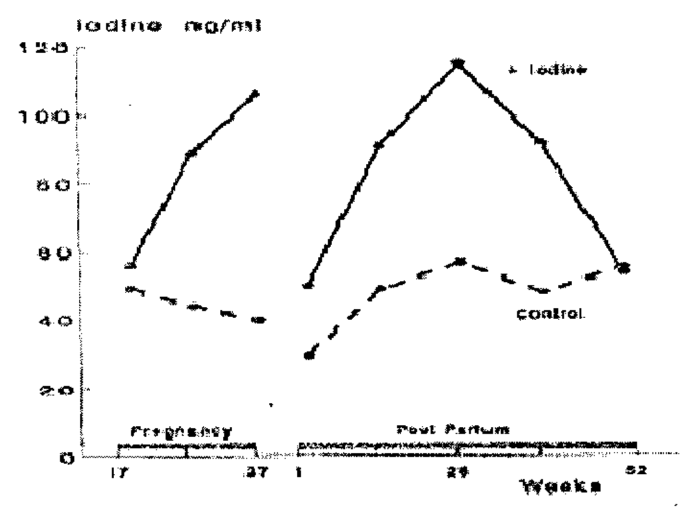

Figure 9. Iodine concentration in spot urine samples during pregnancy and for 52 weeks postpartum in women receiving iodide supplementation and control women. Last sample obtained after iodide supplementation was stopped (Pedersen *et al.*, 1993).

Iodine did not induce significant variations in serum T4, T3 or free T4. Pedersen *et al.* (1993) concluded that a relatively low iodide intake during pregnancy leads to thyroid stress, with increases in Tg release and thyroid size. It is important to note that even in the iodide-supplement group, there was a significant increase in thyroid volume during pregnancy. Notably, the size of the thyroid returned to initial values one year after delivery independent of iodide supplement. Pedersen *et al.* (1993) were concerned that thyroidal stress during pregnancy in an area of iodine deficiency can lead to goiter, which is primarily reversible, as was shown in the study. However, at some point iodine deficiency triggers, by an unknown mechanism, irreversible changes in the thyroid with autonomous growth and function and may lead to high incidence of multinodular toxic goiter[4] in elderly subjects. It was suggested that iodine deficiency during pregnancy or even during fetal life could be an important factor for the late development of thyroid autonomy.

Glinoer *et al.* (1995) studied a group of euthyroid pregnant women with mild to moderate iodine deficiency and found pregnancy stresses on the thyroid could be prevented by the administration of potassium iodine or potassium iodine plus L-T4. They selected 180 pregnant women at the end of the first trimester on the basis of biochemical criteria of excessive thyroid stimulation, defined as serum thyroglobin > 20 μg/L associated with a low normal free T4 index (<1.23) and/or an increased T3/T4 ratio ($>25x10^{-3}$). The subjects were randomized in a double blind protocol into three groups and treated until term with a placebo (Group A), potassium iodine (100 μg/day) (Group B) or potassium iodine (100 μg/day) plus L-T4 (100 μg/day) (Group C). At the beginning of the study, all the subjects were mildly or moderately iodine deficient as indicated by a median urinary iodine concentration of 36 μg/L, with 56 percent below 40 μg/L, 34 percent between 41-80 μg/L, and only 10 percent between 81-160 μg/L. After therapy was instituted, urinary iodine concentration of Groups B and C rose significantly (to approximately 75-130 μg/L) in the second and third trimesters; while urinary iodine of Group A remained low during gestation and at delivery.

Study results showed that total T4 levels of all groups increased during the second and third trimesters compared to those measured during the first trimester. However, the increases observed in Group A (4 percent and 7 percent for the second and third trimesters, respectively) were much smaller than those observed in Group B (9 percent and 11 percent) and Group C (19 percent and 15 percent). Glinoer *et al.* (1995) also reported that in Groups A and B, the ratios of T3/T4 were higher than normal at the start of the therapy and remained elevated during gestation. In contrast, the ratios decreased rapidly toward normal and were maintained at an level of approximately $22x10^{-3}$ in Group C. These results indicated that thyroid stimulation associated with pregnancy and leading to preferential T3 secretion by the thyroid was suppressed after potassium iodide plus L-T4 administration. Glinoer *et al.* (1995) found an average increase of 30 percent in thyroid volume in Group A. Sixteen percent of the women in this group developed a

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[4] Multinodular toxic goiter is usually found in older persons who had a goiter for a long time. Histologically, the nodules are follicular adenomas. The illness is characterized by suppressed TSH levels and marked elevation of T3 levels, with T4 levels showing a lesser increase. Antibodies against the TSH receptor and thyroid peroxidase are absent, in contrast to patients with Graves' disease.

goiter during gestation, with thyroid volume up to 34 mL at delivery. The increment in thyroid volume was much less in Group B (mean increase of 15 percent) and in Group C (mean increase of 8 percent). Furthermore, goiter formation in Groups B and C was less frequent than that in Group A, as it was observed in only 10 percent and 3 percent of the cases, respectively. In the same study, Glinoer *et al.* (1995) also evaluated the thyroid status of the newborns, 3-6 days after delivery. They found the mean thyroid volume of newborns in Group A (1.05±0.05 mL) was significantly larger than those in Groups B (0.76±0.05 mL) and Group C (0.75±0.05 mL). Furthermore, glandular hyperplasia (thyroid volume >1.4 mL) was found in 10 percent of newborns in Group A (range 1.5-2.2 mL) compared to none in Groups B and C (p=0.01, by χ^2 test). Glinoer *et al.* (1995) found the study results in agreement with other investigations on goitrogenesis during pregnancy in areas with less than adequate iodine supply. They attributed the significantly study findings on the goitrogenic role of pregnancy to the selection of pregnant women at the extreme fringe of the population.

Rotondi *et al.* (2000) reported that in areas of moderate iodine deficiency, there is a significant association between a larger thyroid size, in healthy women, with the number of their previous pregnancies. They studied the size of thyroids of 208 nongoitrous healthy females by ultrasound examination. All subjects lived in a region (Naples, Italy) that is known to have moderate iodine deficiency, with usual urinary levels ranging from 40-100 µg/day. All subjects underwent serum free T3, free T4, and TSH determinations, as well as thyroglobulin antibody and thyroid peroxidase antibody detection. All subjects were clinically and biochemically euthyroid and had no detectable thyroid autoantibodies. The subjects were divided into five groups, according to the number of completed pregnancies (0, 1, 2, 3, 4 or more term pregnancies). The researchers found mean thyroid volume increased progressively among the groups; group 0 (14.8±0.7 ml); group I (16.0±0.9 ml); group II (17.1±0.6 ml); group III (18.2±0.6 ml); group IV (20.3±0.9 ml). The increase in thyroid volume was statistically significant between group 0 and groups III (p<0.01) and IV (p<0.001), and also between group I and group IV (p<0.05). No independent effect of body weight and age on thyroid volume was seen. Based on the results, Rotondi *et al.* (2000) suggested that, in an area with moderate iodine deficiency, there is a cumulative goitrogenic effect of successive pregnancies and the goitrogenic effect of pregnancy is not fully reversible.

However, a survey of the scientific literature shows that not all researchers found an association between pregnancy and enlarged thyroids. Gerghout *et al.* (1994) studied 10 healthy women before and during a normal pregnancy in an iodine replete area of Amsterdam, the Netherlands. They found no change in thyroid volume during pregnancy (data given before pregnancy and during first, second, and third trimesters, respectively: 10.3±5.1, 10.6±4.4, 9.6±3.8, and 9.4±3.0 mL. Urinary iodine levels were not measured and dietary iodide intake levels were not estimated by the authors.

Long *et al.* (1985) studied a group of pregnant teenagers and found the frequency of goiter in this group was not higher than that in non-pregnant teenagers. They studied 309 consecutive pregnant adolescent girls who were admitted to a medical center in San Diego, California from August 1978 through December 1982. A group of 600 adolescent girls was used as controls to establish the prevalence of goiter in non-pregnant adolescents. The mean gestational age for the first visit was 22 weeks. A thyroid gland was defined as enlarged if it was visible and/or palpable and having a transverse span of ≥ 6 cm. Eighteen goiters (6 percent) were identified in the pregnant teenagers versus 27 goiters (5 percent) in the control group. It should be noted that the detection method used in the study is not as sensitive and reliable as the ultrasound detection used in the more recent studies. Long *et al.* (1985) concluded that abnormalities of size and function of the thyroid gland were not more prevalent during the stress of reproduction at a young age.

Levy *et al.* (1980) examined the thyroid glands of 49 matched pairs of women in Ohio, one pregnant and one non-pregnant woman per pair. All pregnant women were at least 20 weeks into the pregnancy and had no personal history of thyroid abnormality. The subjects were paired by race and age (within 5 years) and examined by multiple observers. Observers independently graded each thyroid as "not palpable," "palpable but not enlarged," or "enlarged;" they also compared the size of the two glands relative to one another for every pair of subjects. Levy *et al.* (1980) found that in 22 pairs the pregnant woman had the larger thyroid, whereas in 20 pairs the opposite was true. In six pairs the thyroid glands were not palpable, and in one pair the thyroid glands were of equal size. Five pregnant and three nonpregnant women had clinically significant goiters. None of the differences was statistically significant. They suggested that goiter in pregnancy should be considered to be a pathologic condition in an iodide-replete population. These results are consistent with the study of Crooks *et al.* (1967) conducted in Reykjavik, Iceland, which showed that pregnancy did not impact the thyroid gland when iodide intake was adequate.

Liberman *et al.* (1998) studied the serum T4, TSH, and serum and urinary inorganic iodine levels during the first, second, and third trimesters and after delivery of 16 women. They reported significantly higher levels of mean serum T4 during the pregnancy than after delivery. Similar levels of serum TSH, serum inorganic iodine, and urinary iodine were measured during pregnancy and after delivery. It is noted that the daily iodide intakes of the subjects were high, indicated by the relatively high average urinary iodine excretion (459 – 786 µg/day). Liberman *et al.* suggested that pregnancy does not have an important influence on serum inorganic iodine or thyroid status in iodine-sufficient regions. However, they also acknowledged that in iodine-deficient regions, maternal thyroid hormone deficiency is aggravated during pregnancy.

Adverse neurological development in infants born to mothers with iodine deficiency or low thyroid hormone levels

The changes in thyroid function associated with pregnancy are related to increased hormone requirements. The need can only be met by proportional increased hormone production and is dependent upon the availability of iodine in the diet (Glinoer, 2001). For this reason, the National Academy of Sciences determines an Estimated Average Requirement of 160 µg/day and a Recommended Dietary Allowance of 220 µg/day for pregnant women (NAS, 2001). These values are approximately 50 percent higher than the Estimated Average Requirement of 95 µg/day and the Recommended Dietary Allowance of 150 µg/day determined for adults (age 19 years and older).

Iodine deficiency disorders range from the most severe form, endemic cretinism, which is characterized by mental and growth retardation, rigid spastic motor disorders, and deaf mutism; to endemic goiter and less severe forms of brain damage. The impact of iodine deficiency differs depending on the age and life stage of the individual affected as well as the degree of iodine deficiency. The most severe problems caused by iodine deficiency are among fetuses, neonates, and infants because of the irreversible changes that can occur during this period of rapid structural and behavioral development. Cognitive impairment is the most common finding seen with iodine deficiency and thyroid disorders during pregnancy risk causing neurologic damage in their offspring (Hetzel and Maberly, 1986; as cited in Hollowell and Hannon, 1997). It was considered a paradox that in areas of iodine deficiency, children with cretinism, but with functioning thyroid glands, had more severe central nervous system damage than some children who were missing a thyroid gland. For prevention of central nervous system damage, iodide has to be supplied before conception or early in the first trimester, a time in development before the fetal thyroid is known to be functional (Hollowell and Hannon, 1997). The finding that maternal T4 does reach the fetus (Vulsma *et al.*, 1989) made it understandable that thyroid hormones are necessary for brain development during its early developmental period, and severe central nervous system damage can occur as a result of maternal thyroid deficiency.

This theory is supported by the results of a number of animal and human studies. Obregon *et al.* (1984) and Woods *et al.* (1984) showed that fetal rat tissues, including brain, contained T4 and T3 before fetal thyroid hormone was produced. Several researchers also reported that nuclear T3 receptors in brain tissues obtained from rat and human fetuses early in gestation (before the development of the fetal thyroid) were relatively saturated with T3 (Bernal and Pekonen, 1984; Perez Castillo *et al.*, 1985; Ferreiro *et al.*, 1988; as cited in Burrow *et al.*, 1994). The presence of occupied T3 nuclear receptors in brain tissues early in fetal development supports a role for maternal thyroid hormones in the maturation of the brain.

In two animal developmental studies, ammonium perchlorate was administered to female Sprague-Dawley rats via drinking water at target doses between 0.01 and 30 mg/kg-day (Argus Research Laboratories, 1998a; 2001). Morphometric analysis of the pups revealed significant changes in sizes of a number of brain regions (e.g., corpus callosum), although a simple dose-response relationship is not observed in any of the changes (Figure 3).

Severe iodine deficiency has been shown to cause abnormal fetal brain development in a number of animal species. Potter *et al.* (1982) reported that severe iodine deficiency in sheep caused reduction in fetal brain weights and in brain DNA and protein from 70 days of gestation to parturition. They also found unusual morphological changes in both the cerebral hemispheres and the cerebellum of the fetal brains. Hetzel *et al.* (1987) reported that severe iodine deficiency caused abnormal fetal brain development in rat, marmoset, and sheep. The abnormalities included reduced brain weight, change in cell density in the cerebral hemispheres, reduced synaptic counts in the visual cortex, and reductions of brain DNA and brain protein.

Many human studies have been published that demonstrate maternal thyroid deficiency during pregnancy affects neuropsychological development of the child. Man and Jones

(1969) first reported that maternal hypothyroidism was associated with lower intelligence quotient scores (IQs) in 8-month-old infants. Hypothyroidism was defined in this study by two low serum butanol extractable iodine test values during pregnancy or by one low serum butanol extractable iodine value with clinical hypothyroidism. They found that 81 percent of 26 infants of women given thyroid replacement therapy after two low serum butanol extractable iodine tests were classified "normal," approximately the same percentage as for infants of euthyroid women. In contrast, only 48 percent of the 56 infants of women with two low serum butanol extractable iodine values who were not given adequate thyroid replacement therapy were "normal."

Glorieux *et al.* (1985) reported that children with significantly retarded skeletal maturation at the time of diagnosis, signifying hypothyroidism in utero, obtained lower global IQs than did children whose skeletal maturity was within normal limits. In a later study, Glorieux *et al.* (1988) studied 43 infants with congenital hypothyroidism and found that low T4 (<2 μg/dL) and retarded bone surface (<0.05 cm^2) measurements taken before therapy initiation were strongly correlated with mental development at 3, 5, and 7 years of age (Table 20).

Table 20. Mental Outcome in Infants with Congenital Hypothyroidism Relative to Newborn Risk Criteria (from Glorieux *et al.*, 1988)

Age in years	T4 < 2 μg/dL and bone surface measures < 0.05 cm^2			T4 > 2 μg/dL and/or bone surface measures > 0.05 cm^2		
	n	Mean IQ	IQ distribution	n	Mean IQ	IQ distribution
3	17	91 ± 4 *	(61 – 120)	40	103 ± 2	(81 – 140)
5	14	88 ± 3 **	(60 – 109)	30	104 ± 2	(84 – 125)
7	16	86 ± 3 **	(49 – 98)	27	102 ± 2	(75 – 128)

* $p < 0.01$ ** $p < 0.001$

Similar findings have been reported by Rovet *et al.* (1987), who studied intellectual and behavioral characteristics at 1, 2, 3, 4, and 5 years of age of 23 boys and 57 girls with congenital hypothyroidism. The children were assigned to two groups based on degree of skeletal maturity at the time of diagnosis. Forty-five children with bone age <36 weeks were assigned to the delayed group; 35 with bone age 37 to term were assigned to the nondelayed group. Both groups were treated for congenital hypothyroidism and the initial starting dosages of L-thyroxine for the delayed and nondelayed were similar, 8.1 mg/kg and 7.8 mg/kg, respectively. Although most children with athyrosis were found in the delayed group, the group did not differ in birth weight, hormone levels, or family background. Hormone levels at diagnosis of both groups are shown in Table 21. Tests showed that although children in the delayed group performed within the normal range, their scores were significantly lower than those of the nondelayed group from age 2 years on. Perceptual-motor, visuospatial, and language areas were most affected (Rovet *et al.*, 1987).

Table 21. Hormone Levels at Diagnosis in Children with Delayed and Nondelayed Skeletal Maturity (from Rovet *et al.*, 1987)

	Delayed (N=45)	Nondelayed (N=35)
	TSH (U/dL)	
Screening	136.1±128.8	130.6±78.6
Confirmation	112.5±119.2	131.9±100.5
	Thyroxine (T4) (μg/dL)	
Confirmation	5.1±4.7	5.5±3.9
1 month	11.0±5.3	10.3±5.7
3 months	12.0±4.5	13.5±3.9
6 months	13.6±2.8	12.6±3.2
9 months	12.4±3.5	14.1±5.3
12 months	12.7±2.7	13.5±2.3

Values represent mean ± standard deviation.
T4 level: 5.1 μg/dL is equivalent to 65.6 nmol/L

Tillotson *et al.* (1994) reported the results of a prospective study of psychological outcomes of 361 children with congenital hypothyroidism after five years of treatment and follow-up. They also selected 315 children as controls, matched for school attended, sex, age (within three months), language spoken at home, and social class defined by occupation of the family breadwinner. Severity of congenital hypothyroidism was assessed from the first quantitative T4 measurement after the positive screening test and before treatment (median age 17 days; range 0-114). The study showed that in children with congenital hypothyroidism and given early treatment there was a sharp threshold in intellectual outcome that divided them into two distinct groups – those with plasma T4 concentrations of less than 42.8 nmol/L (3.3 μg/dL) at diagnosis, who showed a global deficit in mean IQ of 10 points, and those with less severe congenital hypothyroidism, who showed no deficit.

Vermiglio *et al.* (1990) demonstrated that normal euthyroid children conceived and born to mothers exposed in a severe (area A) and less severe (area B) iodine deficiency region in northeastern Sicily showed a defective visual perceptual integrative motor ability. They studied 719 primary schoolchildren (366 males and 353 females) ranging from 6 to 12 years old (i.e., they had been conceived and born between 1975 and 1981). The prevalence of goiter in the schoolchildren and the daily urinary iodine excretion in the general population between 1976 and 1984 are given in Table 22.

Table 22. Prevalence of Goiter in Schoolchildren and Daily Urinary Iodine Excretion in Adults (1976-1984) in the Study Areas (from Vermiglio *et al.*, 1990)

Study area	Total population	Prevalence of goiter in the schoolchildren (%)	Daily urinary iodine excretion (μg/day)*
Area A (with endemic cretinism)	7,432	70.3 (708)	24.3±16.4 (55)
Area B (without endemic cretinism)	10,992	45.9 (763)	31.3±18.7 (150)
Area C (control area)	9,730	8.9 (370)	82.4±43.0 (30)

* Mean±standard deviation; the number of observations is given in parentheses.
The prevalences and daily urinary excretion were established between 1976 and 1979.

Area A vs. area B: χ^2 =112; p<0.001, t =2.43; p<0.05.
Area A vs. area C: χ^2 =111; p<0.000005, t =8.98; p=0.
Area B vs. area C: χ^2 =78; p<0.000005, t =10.55; p=0.

Variable degrees of thyroid enlargement were found in 205 of 719 (28.5 percent) children from both area A and area B (area A: 30.4 percent; visible goiter 15.2 percent; area B 26.5 percent; visible goiter 16.3 percent).

Furthermore, defective visual perceptual integrative motor ability (the Bender Gestalt test) was significantly higher in children from area A (14.4 percent) and area B (13.1 percent) than area C (3.5 percent) (Table 23). The control group consisted of 370 age-matched schoolchildren from an iodine-sufficient goiter-free area (area C).

Table 23. Number of Defective, Borderline, and Nondefective Schoolchildren as Assessed by the Bender Gestalt Test (from Vermiglio *et al.*, 1990)

Performance on Bender	Area A	Area B	Area A+B	Area C
Defective	53 (14.4)	46 (13.1)	99 (13.8)	13 (3.5)
Borderline	57 (15.5)	67 (19.1)	124 (17.2)	14 (3.8)
Nondefective	258 (70.1)	238 (67.8)	496 (69.0)	343 (92.7)
Total	368 (100)	351 (100)	719 (100)	370 (100)

Percent in parentheses. Performance score: defective, below –1 standard deviation from average score of normal children of the same age; borderline, equal to –1 standard deviation from average score; nondefective, higher than –1 standard deviation from average score.
Statistical comparisons:

Defective

Area A vs. area B: χ^2 =2.75; p=0.87 (NS);
Areas A+B vs. area C: χ^2 =36.25; p<0.000001

Borderline

Area A vs. area B: χ^2 =1.22; p=0.27 (NS);
Areas A+B vs. area C: χ^2 =77.55; p<0.000001

In addition, Vermiglio *et al.* (1990) also reported higher frequency of neuromuscular and neurosensorial abnormalities among children from areas A and B (a combined overall prevalence of 18.9 percent). The Terman Merrill test of general intellectual aptitude was administered to 96 of 99 "defective" children and 62 of 124 borderline children from both areas A and B (Table 23). Ninety-one of 96 "defective" children (94.8 percent) had IQs lower than 90, as did 35 of 62 borderline (56.4 percent) children (Table 24).

Table 24. Performance at the Scale Test (Terman Merrill) Administered to Schoolchildren with Defective or Borderline Performance at the Bender Gestalt Test (from Vermiglio *et al.*, 1990)

Performance on Bender test	Intelligence quotient score, <90	Intelligence quotient score, 90-95	Intelligence quotient score, 96-100
Defective (n=96)	91	5	0
Borderline (n=62)	35	23	4
Nondefective (n=12)	0	10	2

Statistical analysis: $\chi^2 = 52.1$; $p<0.0000005$.

Despite the adverse effects observed, Vermiglio *et al.* (1990) found serum T3 and T4 levels of the children from area A and area B were within the normal range. These data suggest serum T3 and T4 are not good indicators of neurological damages caused by iodine deficiency. Vermiglio *et al.* (1990) hypothesized that fetal and postnatal hypothyroidism, maternal hypothyroxinemia, and iodine deficiency are the likely underlying causes of the observed defective neuromotor and cognitive abilities in schoolchildren.

Bleichrodt and Born (1994) performed a meta-analysis on the data from 21 iodine and mental development studies. A study was selected if it contained information on the general cognitive functioning of children and adults living in iodine-deficient areas and if it gave the necessary statistical data. Three of the studies were excluded from the analysis because the composition of the groups studied was different (they were composed exclusively of school children). The remaining 18 studies formed a homogeneous group. In the meta-analysis of the effects of iodine deficiency on cognitive development, a large effect size was found with a d-value of 0.90. This means that the mean scores for the two groups studied, the iodine-deficient group and the noniodine-deficient group, are 0.90 of a standard deviation (or 13.5 IQ points), apart. In other words, a typical child with an average score in the noniodine-deficient group scores higher than 82 percent of the children from the iodine-deficient group, assuming the IQ scores of the two groups are normally distributed.

Pop *et al.* (1999) reported that low maternal free T4 concentrations in apparently healthy women during early gestation implicate a significantly increased risk (RR=5.8) of impaired neurodevelopment in the infant. They studied a group of 291 pregnant women in an iodine-sufficient area (in and around the city of Veldhoven, Netherlands) between January and November 1994. No women in the study group were receiving antithyroid drugs and/or thyroid hormones. Maternal thyroid determinants (free T4, TSH, and thyroid peroxidase antibodies) were assessed at 12 and 32 weeks' gestation, and neurodevelopment of 220 healthy children was assessed at 10 months of age. Pop *et al.* (1999) found that children of women with free T4 levels below the 5th (<9.8 pmol/L, n=11) and 10th (<10.4 pmol/L, n=22) percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Developmental Index scale at 10 months of age, compared to children of mothers with higher free T4 values (t-test, mean difference: 14.1, 95 percent confidence interval: 5.9-22 and 7.4, 95 percent confidence interval: 1.1-13.9, respectively). At 32 weeks' gestation, no significant correlations were found between thyroid hormone levels and test scores.

In another study, Pop *et al.* (2003) reported that maternal hypothyroxinemia during early pregnancy was associated with a delay in infant neurodevelopment. They followed 115 children and their mothers for two years. Maternal hypothyroxinemia was defined as having free T4 below the lowest tenth percentile and TSH within the reference range. All children had normal Apgar scores at birth and normal screening results for congenital hypothyroidism on the seventh postpartum day. Pop *et al.* observed that children of women who had hypothyroxinemia during early gestation and who exhibited a further decrease of free T4 during gestation had the lowest mental/motor scores. In contrast, children whose mother showed early hypothyroxinemia, but whose free T4 levels increased during later gestation, did not show any delay in development.

Haddow *et al.* (1999) measured thyrotropin in stored serum samples collected from 25,216 pregnant women (during the second trimester) in Maine between January 1987 and March 1990. They then located 47 women with serum thyrotropin concentrations at or above the 99.7th percentile of the values for all the pregnant women, 15 women with values between the 98th and 99.6th percentile, inclusive, in combination with low T4 levels. They used 124 matched women with normal thyrotropin levels as controls. Measurements of thyroid function of the women in the study are shown in Table 25. Haddow *et al.* (1999) then administered 15 tests to their seven-to-nine-year-old children, none of whom had hypothyroidism as newborns. The neuropsychological tests included assessment of intelligence, attention, language, reading ability, school performance, and visual-motor performance. The staff giving the tests did not know whether the children's mothers were women with hypothyroidism or control women. They found that children of the 62 women with high serum thyrotropin concentrations performed slightly less well on all 15 tests. Of the 62 women with thyroid deficiency, 48 were not treated for the condition during the pregnancy under study. The full-scale IQ scores of their children average 7 points lower than those of the 124 matched control children (P=0.005). Haddow *et al.* (1999) concluded that that even mild and probably asymptomatic hypothyroidism in pregnant women can adversely affect their children's subsequent performance on neuropsychological tests.

Table 25. Measurements of Thyroid Function in the Study Women During Pregnancy (from Haddow *et al.*, 1999)*

Variable	Hypothyroidism (N=62)	Controls (N=124)
Serum thyrotropin (TSH) level (mU/L)	13.2±0.3 **	1.4±0.2
Serum thyroxine (T4) level (μg/dL)	7.4±0.1 ** (95.2 nmol/L)	10.6±0.1 (136.4 nmol/L)
Serum free thyroxine (T4) level (ng/dL)	0.71±0.1 ** (9.1 pmol/L)	0.97±0.07 (12.5 pmol/L)

* Values are geometric means ± the logarithmic standard deviation.
** <0.001 for the comparison with the control women.
To convert serum T4 from μg/dL to nmol/L or free T4 from ng/dL to pmol/L, multiply by 12.87.

In a follow-up study, Klein *et al.* (2001) studied serum TSH concentrations of pregnant mothers at a mean of 17 weeks gestation and the standard neuropsychological testing results of their offspring at a mean age of 8 years. They found there was an inverse correlation between the severity of maternal hypothyroidism and IQs in the offspring and suggested that the result supports a causal association of maternal hypothyroidism and poor cognitive development of offspring. Klein *et al.* (2001) divided the mothers and their offspring into three groups: group 1, 124 control mothers with TSH concentrations <98th percentile; group 2, 28 hypothyroid mothers with TSH concentrations between the 98th and 99.85th percentile; group 3, 20 hypothyroid mothers with TSH concentrations ≥99.85th percentile. Mothers treated for hypothyroidism during pregnancy were excluded from the study. They found the mean (standard deviation) for the children of the 124 control mothers was 107 (12). Means (standard deviation) for the children in groups 2 and 3 were 102 (15) and 97 (14), respectively. The difference between the children in group 3 mothers differed significantly from those of group 1 mothers (p=0.003). The mean for group 2 children was intermediate between those for the group 1 and group 3 children but not statistically significantly different from either. The incidences of IQs greater than one standard deviation below the control mean were 15 percent, 21 percent, and 50 percent for the children in group 1, group 2, and group 3, respectively. In a related study, the same authors also reported spontaneous abortions and intra-uterine fetal deaths were more than five times as common in the mothers with TSH concentrations above the 98th percentile than in control mothers with TSH concentrations below the 98th percentile.

Not all researchers have found an association between fetal hypothyroidism and impaired brain development. Several studies examined children exposed to antithyroid drugs such as carbimazole, propylthiouracil, or thiamazole[5] in utero and did not find an association between the treatment and the later intellectual and somatic development of the children

[5] Thiouracils and imidazoles are two groups of antithyroid drugs that inhibit thyroid hormones production by interferring the iodination of tyrosine.

(McCarrol *et al.*, 1976; Burrow *et al.*, 1978; Messer *et al.*, 1990). The powers of these studies are limited as they have relatively small sample size and the dosage and timing of the treatment were not known in many cases. In the study reported by Burrow *et al.* (1978), most of the treated children were exposed to propylthiouracil in utero during the third trimester and only four were exposed during the first and second trimester. The studies reported by Burrow *et al.* (1978) and Messer *et al.* (1990) were retrospective studies where maternal T4 levels during the first and second trimesters were not known. It is possible that the treated women had normal T4 levels during the early part of their pregnancies.

Fenzi *et al.* (1990) conducted neuropsychological assessments on a group of 384 school children (aged 6-14 years) residing in an area of known iodine deficiency (Tuscany, Italy). Another group of 352 sex- and age-matched schoolchildren of a control iodine sufficient area was used as control. Goiter prevalence in the endemic and control areas was 51.9 percent and 5.6 percent, respectively. No significant differences in serum total T4, total T3, TSH levels between the endemic and control areas were found. Serum thyroglobulin values were significantly higher in the iodine-deficient area. Global neuropsychological performance and cognitive levels were similar between a group of 50 schoolchildren from the endemic area and another group of 50 schoolchildren from the control area, matched for age, sex and socioeconomic conditions. However, Fenzi *et al.* (1990) also found that some marginal impairment, with particular regard to motor-perceptual functions, was present in areas of moderate iodine deficiency.

New England Congenital Hypothyroidism Collaborative Program (1981) found that there was no correlation of eventual IQs with the severity of the thyroid dysfunction or with the results of biochemical tests at the time treatment was begun, provided it was begun before clinical hypothyroidism appeared. A diagnosis of hypothyroidism was made when an infant's initial blood concentration of T4 was two or more standard deviations below the mean for newborn infants (6 μg/dL or less) and circulating TSH concentrations were elevated on repeated occasions. 336,000 newborn infants in Connecticut, Maine, Massachusetts, New Hampshire, and Rhode Island born between January 1, 1976 and June 30, 1978 were screened. Sixty-three infants were diagnosed with hypothyroidism and treated with L-thyroxine in doses sufficient to maintain circulating T4 concentration between 10 and 14 μg/dL during the first year of life and between 8 and 11 μg/dL thereafter. The control group consisted of 57 euthyroid children who had low T4 and normal TSH concentrations on neonatal screening. The revised Stanford-Binet examination was given to all the test subjects at 3 or 4 years of age. The authors reported that the mean IQs for the hypothyroid infants with adequate thyroid treatment was 106 ± 16 and the mean for the controls was 106 ± 15. They also reported that half of the patients with the lowest IQs (more than one standard deviation below the mean) had normal bone maturation. It is important to note that the results of Pop *et al.* (1999) indicated that it is the low maternal T4 level during early gestation (around week 12) that is associated with impaired neurodevelopment in the infant. Serum T4 levels at birth may not be a good indicator for neurodevelopment in early gestation.

Liu *et al.* (1994) examined IQs of eight children (Group 1) who were born to eight mothers that were hypothyroid during the first trimester of pregnancy. Maternal free T4 values at the fifth to 10^{th} gestation weeks ranged from 2.3 to 6.3 pmol/L (normal range, 11.6 to 24.5 pmol/L) in six of the eight cases. In the other two cases, maternal total T4 values were 52.8 and 30.9 nmol/L (normal range, 92.7 to 218.8 nmol/L). TSH levels of the eight mothers at that time ranged from 25 to 190 mU/L (normal range < 5 mU/L). Maternal T4 and TSH levels became normal after T4 supplementation by 13 to 28 weeks of gestation. Seven of the eight children had nine siblings who had not been exposed to maternal hypothyroidism throughout gestation (Group 2); they were used as controls. Ages of the children in groups 1 and 2 at the time of IQ examination were 4 to 10 years in group 1 and 4 to 15 years in group 2. The investigators reported that all children in group 1 showed normal IQs. There was no significant difference in the mean IQ between the children in group 1 who had siblings (112±11) and their siblings in group 2 (106±8). The study is limited by the small sample size. The administration of T4 supplement to hypothyroid mothers at 13 weeks of gestation might have averted adverse neurological development in the fetuses.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Animal data

As discussed earlier in this document, one of the main effects of perchlorate exposure, especially at low doses, is the disruption of thyroid hormone regulation. This mode of action is supported by results from a number of animal studies that showed perchlorate inhibits thyroidal iodide uptake; changes serum T3, T4, and TSH levels; causes thyroid enlargement; induces thyroid follicular cell hypertrophy and hyperplasia; and increases the risk of thyroid tumors.

Adult rodents are found to be more susceptible than adult humans to the perturbation of thyroid hormone homeostasis by short-term exposure to perchlorate. Significant changes in serum T3, T4, and TSH levels were observed even at the 0.01 to 0.1 mg/kg-day dose range. Rat fetuses and rat pups are reportedly more sensitive to the effects of perchlorate than adult rats. In several reproductive and developmental studies, colloid depletion of the thyroid, thyroid hypertrophy, and abnormal brain development were found in rat pups exposed to perchlorate in utero and after birth. Based on these study results (Springborn Laboratories, 1998; Argus Research Laboratories, 2001), a LOAEL of 0.01 mg/kg-day can be identified.

Using data derived from animal studies, Clewell *et al.* (2003) developed a PBPK model to predict the distribution and the NIS inhibition effect of perchlorate in rats of different life stages (e.g., adult male, pregnant female, fetus, lactating female, and neonate). The model predicted that the fetal rat thyroid is most vulnerable to the inhibitory effect of perchlorate on the uptake of iodine by the thyroid.

Human data

According to the California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365), in the development of PHGs OEHHA is required to consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.

In his review paper, Glinoer (2001) suggested that pregnancy causes profound changes in thyroid function and represents a stress on the thyroid hormonal system. In the first trimester of gestation, there is an increased need of thyroid hormones that in turn depends upon the availability of iodine in the diet. When iodine nutrition levels are sufficient, physiological adaptation takes place. When iodine is restricted or deficient, adequate physiological adaptation is difficult to achieve and is progressively replaced by pathological alterations occurring in parallel with the degree of long-term iodine deprivation. He concluded, "Therefore, pregnancy typically reveals underlying iodine restriction and gestation results in an iodine-deficient status, even in conditions with only a marginally restricted iodine intake, such as is observed in many European regions."

Results of a prospective study reported by Kung *et al.* (2000) showed that in a borderline iodine-sufficient area (median urinary iodine level = 9.8 μg/dL), pregnancy can pose a stress on the thyroid, resulting in higher rates of maternal goitrogenesis as well as neonatal hypothyroxinemia and hyperthyrotrophinemia. It was also noted that thyroid enlargement in these women persisted and failed to revert completely even 3 months after delivery.

There are several epidemiological studies indicating that iodine deficiency during pregnancy may adversely affect brain development and cause neurointellectual deficits in the offspring. These effects are not limited to areas with severe iodine deficiency and endemic cretinism. The severity of effects appears to depend on the timing and the severity of iodine deficiency and thyroid disorder. In several studies conducted in areas with moderate or even mild iodine deficiency, mainly from southern Europe, it was shown that developmental abnormalities may also occur in clinically euthyroid schoolchildren. Even borderline iodine deficiency, as observed in some European countries, may be accompanied by impaired school achievements in apparently normal children (Glinoer, 2001).

These studies suggest pregnant women and their fetuses are more sensitive to the anti-thyroid effects of perchlorate, especially when the supply of iodine is less than ideal.

Potential low iodide intakes in women of childbearing age

Urinary iodine concentration is an indicator of the adequacy of iodide intake for a population. The median urinary iodine concentrations in iodine-sufficient populations should be greater than 10 μg/dL, and no more than 20 percent of the population should have urinary iodine concentration less than 5 μg/dL (WHO, 1994; as cited in Hollowell *et al.*, 1998). Median urinary iodine concentrations (spot urine samples) from both the National Health and Nutrition Examination Surveys [NHANES I (1971-1974) and NHANES III (1988-1994)] indicate adequate iodide intake for the overall U.S. population, but the median (±standard error) concentration decreased more than 50 percent between 1971-1974 (32.0±0.6 μg/dL) and 1988-1994 (14.5±0.3 μg/dL)

(Hollowell *et al.*, 1998). Low urinary iodine concentrations (<5 μg/dL) were found in 11.7 percent of the 1988-1994 population, a 4.5-fold increase over the percent in the 1971-1974 population. The percentage of people excreting low concentrations of iodine (urinary iodine <5 μg/dL) increased in all age groups. In pregnant women, 6.7 percent, and in women of childbearing age, 14.9 percent had UI concentration below 5 μg/dL (Table 26). Focusing on the Western region of the U.S., the results are about the same; median urinary iodine concentration was 15.3±1.0 μg/dL and the fraction of people excreting low concentrations of iodine (urinary iodine <5 μg/dL) was estimated to be approximately 12.7 percent.

It is important to realize that variability of iodine concentration in spot urine samples is likely to be larger than variability of the average annual urinary iodine. This has been illustrated by a study reported by Andersen *et al.* (2001). Serum T4, T3, and TSH as well as urinary iodine excretion were measured longitudinally for a year in a group of 15 healthy men living in an area of mild to moderate iodine deficiency. Andersen *et al.* (2001) found that the variation around the mean urinary iodine concentration was 2.4 times larger when calculated for the 180 individual urine samples than when calculated for the 15 average annual values. Therefore, the fact that 14.9 percent of the spot urine samples collected from women of childbearing age had iodine concentration less than 5 μg/dL does not necessarily mean that 14.9 percent of them were iodine deficient.

Table 26. Median Concentrations of Urinary Iodine in U.S. Women of Child-Bearing Age (15-44 year) in 1988-1994, and Percentage Who Had Urinary Iodine Levels Below 5 μg/dL or Iodine/Creatinine Levels Below 50 μg/g Creatinine (Hollowell *et al.*, 1998; NHANES III Survey Results)

	Sample number	Urinary iodine		Iodine/creatinine	
		median	% < 5 μg/dL	median	% < 50 μg/g
Total	5405	12.8±0.4	14.9±1.1	113.1±3.2	8.2±0.9
Known pregnant	348	14.1±1.4	6.9±1.9	132.2±11.9	5.1±1.9
Not pregnant	5057	12.7±0.4	15.3±1.2	111.9±3.2	8.4±0.9

Mean±standard error

According to the NHANES III data, the median urinary iodide in women of childbearing age (15-44 years) was 12.8 μg/dL. Using an equation linking urinary iodine and daily iodine intake and assuming a body weight of 58 kg for an adult female (ICRP, 1974), a median dietary iodide intake[6] of 174 μg/day can be estimated. Alternatively, if one assumes the 24-hr urine volume for adults is approximately 1.5 L (NAS, 2001), the median urinary iodine of 12.8 μg/dL is roughly equivalent to a median dietary iodide of

[6] Daily iodine intake [μg] = urinary iodine [μg/L] x 0.0235 x body weight [58 kg]) (NAS, 2001).

192 μg/day. These median estimates are very close to or within the 175-200 μg/day range recommended for pregnant women by the World Health Organization (Delange and Bürgi, 1989; as cited in Caron *et al.*, 1997). The National Academy of Sciences determined an Estimated Average Requirement of 160 μg/day and a Recommended Dietary Allowance of 220 μg/day for pregnant women (NAS, 2001). The comparison shown here indicates that while most of the women in the survey received enough iodine to meet the average requirement of 160 μg/day, many were receiving less than the recommended dietary allowance of 220 μg/day.

There are data to indicate that there may be seasonal variations in dietary iodide intake. Hetherton *et al.* (1991) measured monthly urinary iodine excretion from consecutive patients (n=448) in a medical center in Dublin, Ireland for a year. They found a monthly variation in mean urinary iodine excretion, being lowest at 53 μg/g in July compared to a high of 104 μg/g in April. Similar differences were also observed in a group of schoolchildren (n=131) sampled both in summer (74±27 μg/g) and winter (138±78 μg/g) ($p<0.01$). Hetherton *et al.* (1991) reasoned that since milk consumption was the major source of dietary iodide, seasonal variation in milk iodide was appropriate to examine in the study area of Ireland. They found that the monthly variations in iodine in dietary milk paralleled those in urinary iodine excretion, being lowest at 44 μg/L in June and highest at 222 μg/L in February. If a similar seasonal variation in dietary iodide intake exists in the U.S., women pregnant during the months when dietary iodide intake is relatively low could be more susceptible to perchlorate exposure compared with those who are pregnant during the other months of the year.

In consideration that: (1) women with marginally adequate iodide intake are susceptible to hypothyroxinemia and hypothyroidism during pregnancy; (2) there is a possibility that some women in the child-bearing age in the U.S are getting less than the recommended daily iodide intake level; (3) iodide deficiency during early pregnancy may cause neurointellectual deficits in offspring, and (4) exposure to perchlorate is likely to further reduce iodide uptake by the thyroid, OEHHA recommends that perchlorate in drinking water should be kept at a level that does not inhibit iodide absorption by the thyroid.

A number of rat and human studies (Yu *et al.*, 2000; Lawrence *et al.*, 2000, 2001; Greer *et al.*, 2002) have documented the inhibitory effect of perchlorate on iodide uptake by the thyroid; they have been described in this document. To determine a level of perchlorate exposure that would not inhibit thyroidal iodide uptake, OEHHA chose the Greer *et al.* (2002) study as the critical study and applied the benchmark dose approach for the identification of the point of departure. OEHHA used the BenchMark Dose Software, version 1.3.1 provided by U.S. EPA (2002) to perform the analyses based on the human data reported by Greer *et al.* (2002) shown in Table 27. A detailed discussion of the application of the software is provided in a draft U.S. EPA (2000) document, "Benchmark Dose Technical Guidance Document, External Review Draft."

OEHHA tried several curve fitting models provided by the software and found the Hill model[7] adequately describes the data (goodness of fit test, p=0.46), shown plotted in Figure 10. The fit is generally considered adequate when the p-value is greater than 0.05.

The form of the response function estimated by the model is as follows:

Response = intercept + (v × dose^n) / (k^n + dose^n)

where:

intercept = 0
v = -73.4469
n = 1.15067
k = 0.0663651.

Table 27. Benchmark Dose Modeling of the Human Data of Greer *et al.* (2002)

Average dose (mg/kg-day)	Change in 24 hr radioactive iodine uptake by the thyroid (%)		Number of subjects in each dose group
	Average	Standard deviation	
0.007	-1.844	22.019	7
0.02	-16.393	12.828	10
0.1	-44.693	12.32	10
0.5	-67.076	12.114	10

[7] The Hill model was run with the following settings: intercept = zero, power parameter restricted to be greater than one, a constant variance model assumed.

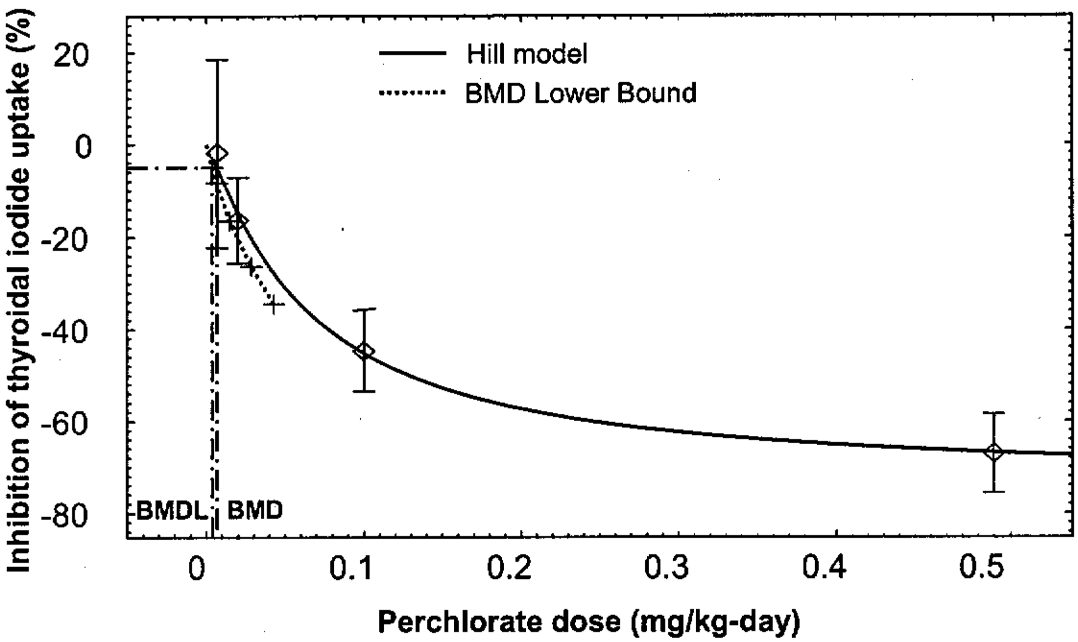

Figure 10. Analysis of the Greer *et al.* (2002) data by the benchmark dose approach.

Two approaches have been suggested by U.S. EPA (2000) for identification of the point of departure for continuous data:

(a) a minimal level of change in the response that is generally considered to be biologically significant; and

(b) a change in the mean equal to one control standard deviation from the control mean.

For this analysis, a five percent decrease of mean radioactive iodine uptake by the thyroid is defined as the point of departure or the benchmark dose (BMD). Approach (a) is selected over approach (b) for this data set because there is no control group in the Greer *et al.* (2002) study. The standard deviation estimated from the lowest exposed group, 0.007 mg/kg-day, is relatively large because it includes both interindividual variability and day-to-day intraindividual variability.

The lower limit of a one-sided 95 percent confidence interval on the BMD can be defined as the BMDL. The estimated BMD and BMDL corresponding to a five percent reduction of the mean thyroidal iodide uptake are 0.0068 mg/kg-day and 0.0037 mg/kg-day, respectively. It should be noted that the BMDL of 0.0037 mg/kg-day is lower than the lowest dose tested, 0.007 mg/kg-day, in the Greer *et al.* (2002) study.

U.S. EPA recommends benchmark dose methods to estimate reference doses (RfDs), which are used along with other scientific information to set criteria and standards for noncancer human health effects. Until recently, RfDs have been determined from NOAELs, which represent the highest experimental dose for which no adverse health effects have been documented. Using the NOAEL in determining RfDs has long been recognized as having limitations in that it 1) is limited to one of the doses in the study and is dependent on study design; 2) does not account for variability in the estimate of the dose-response; 3) does not account for the slope of the dose-response curve; and 4) cannot be applied when there is no NOAEL, except through the application of an uncertainty factor. A goal of the benchmark dose approach is to define a starting point of departure for the computation of a reference value (RfD) or slope factor that is more independent of study design. OEHHA agrees with U.S. EPA on this issue and uses a BMDL of 0.0037 mg/kg-day as the point of departure in the quantitative human health risk assessment of perchlorate.

Carcinogenic Effects

There are two published epidemiological studies investigating the association between perchlorate in drinking water and cancer (Li *et al.*, 2001; Morgan and Cassady, 2002). Based on the reported data, it does not appear perchlorate was associated with increased risks of cancer in the two study areas during the study periods, under the limitations of the studies.

Several subchronic oral studies in rodents showed that perchlorate induced hypertrophy and hyperplasia in the thyroid gland (Caldwell *et al.*, 1995; Springborn Laboratories, 1998; Argus Research Laboratories, 1998b,d, 1999, 2001; Keil *et al.*, 1998). In two chronic oral studies, perchlorate at relatively high concentrations (over 1,000 mg/kg-day) was shown to produce tumors in rats (Kessler and Kruskemper, 1966) and mice (Pajer and Kalisnik, 1991). However, only benign tumors were observed in the study reported by Kessler and Kruskemper (1966), and inadequate reporting and low survival of the control and exposed animals lowered confidence in the results reported by Pajer and Kalisnik (1991). In a developmental study reported by Argus Research Laboratories (1999), thyroid follicular cell adenomas were observed in two male Sprague-Dawley rats (2/30) exposed to 30 mg/kg-day perchlorate in utero and after birth. No such tumors were found in the vehicle control (0/30). Though the incidence is not significant using standard tests (e.g., Fisher's exact test), the fact that the tumors were found in 19-week old rats and the historical incidence of this type of tumor in male Sprague-Dawley rats in 2-year studies reported in the literature is only 3-4 percent makes the finding noteworthy (U.S. EPA, 2002).

Complex anions structurally similar to perchlorate, such as pertechnetate (TcO_4^-), perrhenate (ReO_4^-) and tetrafluoroborate (BF_4^-), are also capable of inducing thyroid follicular cell neoplasia in test animals (Green, 1978, as cited in Paynter *et al.*, 1988). Based on the limited data available, there are reasons to believe that perchlorate is a potential carcinogen in rodents. .

After reviewing thyroid carcinogenesis in rodents and in humans, U.S. EPA (1998b) in the "Assessment of Thyroid Follicular Cell Tumors" stated that "in spite of the potential qualitative similarities, there is evidence that humans may not be as sensitive quantitatively to thyroid cancer development from thyroid-pituitary disruption as rodents. Rodents readily respond to reduced iodide intake with the development of cancer, humans develop profound hyperplasia with "adenomatous" changes with only suggestive evidence of malignancy. Even with congenital goiters due to inherited blocks in thyroid hormone production, only a few malignancies have been found in humans."

One factor that may play a role in interspecies quantitative sensitivity to thyroid stimulation deals with the influence of protein carriers of thyroid hormones in the blood. In humans, other primates, and dogs there is a high affinity binding protein, thyroxine-binding globulin, which binds T4 (and T3 to a lesser degree); this protein is missing in rodents, rabbits and lower vertebrates. As a result, T4 bound to proteins with lower affinity in the rodent is more susceptible to removal from the blood, metabolism, and excretion from the body. As shown in Table 28, the estimated serum half-life of T4 is much shorter in rats (<1 day) than in humans (5-9 days). The much shorter T4 half-life in rats requires a higher level of serum TSH and T4 production rate than in the adult human (U.S. EPA, 1998b). Thus, it appears that the rodent thyroid gland is chronically stimulated by TSH levels above basal levels to compensate for the increased turnover of thyroid hormones, and this in turn could move the gland towards increased growth and potential neoplastic change more readily than in humans. It is interesting to note that adult male rats have higher serum TSH levels than females, and they are often more sensitive to goitrogenic stimulation and thyroid carcinogenesis. In humans, there is no sex difference in hormone levels, but females more frequently develop thyroid cancer (U.S. EPA, 1998b).

The quantitative difference in the thyroid responses of humans and rodents to perchlorate is also evident in the data provided in this document. Several 14-day drinking water studies showed significant depression in serum T3, T4, and elevation in serum TSH levels in rodents exposed to doses as low as 0.01 or 0.1 mg/kg-day (Caldwell *et al.*, 1995; Springborn Laboratories, 1998; Keil *et al.*, 1998; Yu *et al.*, 2000). By contrast, serum T3, T4, and TSH levels in humans that are not iodine deficient are much less sensitive to perchlorate exposure. For instance, after exposure to perchlorate in drinking water as high as 12 mg/kg-day for 1, 2, or 4 weeks, no significant changes in serum T3 and T4 levels were found in male volunteers. Serum free T4 and TSH levels were significantly depressed following perchlorate exposure when compared to those before exposure (Brabant *et al.*, 1992; Mattie, 2000). A significant reduction in intrathyroidal iodine concentration was also noticed in the study reported by Brabant *et al.* (1992). Lawrence *et al.* (2000) found no change in serum T3, T4, and TSH in male volunteers exposed to perchlorate in drinking water at 0.14 mg/kg-day for 1 and 2 weeks. Greer *et al.* (2002) exposed male and female volunteers to perchlorate in drinking water at 0.02, 0.1, or 0.5 mg/kg-day for 2 weeks and collected blood samples on day 1, 2, 3, 4, 8, and 14. No significant depression in serum T3 and T4 nor elevation in serum TSH was observed. No dose-response relationships were noticed for these thyroid and pituitary hormones. These data show that though a similar mode of action of perchlorate is operative in rodents and humans, the sensitivities of serum T3, T4, and TSH levels of the two species to perchlorate may not be the same.

Table 28. Inter- and Intraspecies Differences of T3, T4, and TSH Levels and Sensitivity to Thyroid Cancer (Modified from U.S. EPA, 1998b)

Parameter	Human	Rat
Thyroxine-binding globulin	present	Essentially absent
T4 half-life	5-9 days	0.5-1 day
T3 half-life	1 day	0.25 day
$\frac{\text{T4 production rate}}{\text{kg body weight}}$	1 ×	10 × that in humans
TSH	1 ×	6-60 × that in humans
Follicular cell morphology	Low cuboidal	cuboidal
Sex differences		
Serum TSH	Sexes equal	Male $\leq$ 2 × Female
Sensitivity to thyroid cancer	Female = 2.5 × Male	Male > Female

As U.S. EPA (1998b) described in the "Assessment of Thyroid Follicular Cell Tumors," it is presumed that chemicals that produce rodent thyroid tumors may pose a carcinogenic hazard for the human thyroid, and in the absence of chemical-specific data, humans and rodents are presumed to be equally sensitive to thyroid cancer due to thyroid-pituitary disruption. This is a conservative position when thyroid-pituitary disruption is the sole mode of action, because rodents appear to be more sensitive to this carcinogenic mode of action than humans.

In evaluating a thyroid carcinogen, it is important to determine the mode of action as it impacts the choice of models in high-to-low dose extrapolation. In the "Assessment of Thyroid Follicular Cell Tumors," U.S. EPA (1998b) stated that in order to show the antithyroid activity of a chemical is the cause of thyroid tumors observed in rodents, it is necessary to demonstrate the following:

1. increases in thyroid growth;
2. changes in thyroid and pituitary hormones (considered to be the most important);
3. location of the sites of antithyroid action (documents where in the body the chemical under assessment leads to perturbations in thyroid-pituitary function);
4. dose correlations among various effects (to determine where the growth curve for the thyroid gland deviates from the normal pattern of cell replacement and how this relates to doses producing tumors); and
5. reversibility of effects following treatment cessation during the early stages of disruption of the thyroid-pituitary axis (shows that permanent, self-perpetuating processes have not been set into motion).

The available toxicity data of perchlorate appear to have fulfilled the five requirements described above. Several *in vitro* and *in vivo* genotoxicity studies have been performed on perchlorate. Under the testing conditions, none of the tests indicates perchlorate is a genotoxic agent. Perchlorate is known to inhibit the uptake of iodide in the thyroid, thereby causing a reduction in the hormones T3 and T4. Subchronic and chronic drinking water studies showed that perchlorate exposure depressed serum T3 and T4 but elevated serum TSH levels in rodents and rabbits. At higher exposure levels, thyroid follicular cell hypertrophy, thyroid follicular cell hyperplasia, and increased thyroid weights were also observed in adults as well as postnatal rats (see "Subchronic Toxicity" and "Developmental and Reproductive Toxicity").

There is also evidence that the thyroid follicular cell hypertrophy and hyperplasia observed in rats exposed to ammonium perchlorate might be reversible. In the study reported by the Springborn Laboratories (1998), absolute and relative thyroid/parathyroid weights were significantly increased in male rats exposed to 10 mg/kg-day for 14 days as well as 90 days. However, no significant increases in both absolute and relative thyroid/parathyroid weights were observed in male rats exposed to 10 mg/kg-day for 90 days, followed by a 30-day recovery period. Similarly, absolute and relative thyroid/parathyroid weights were significantly increased in female rats exposed to 10 mg/kg-day for 90 days, but no significant increases in terms of both absolute and relative thyroid/parathyroid weights were observed in female rats exposed to 10 mg/kg-day for 90 days, followed by a 30-day recovery period.

The available data indicate thyroid tumors observed in rodents exposed to perchlorate via the oral route are likely to be caused by the disruption of thyroid-pituitary homeostasis. It follows that if there were no thyroid and pituitary hormone changes, no thyroid follicular cell hypertrophy and hyperplasia, there would be no thyroid tumors. For this reason, the perchlorate dose determined for prevention of inhibition of thyroidal iodide uptake in humans (non-carcinogenic effect) is reasoned to be protective against thyroid tumors as well.

CALCULATION OF PHG

Noncarcinogenic Effects

As perchlorate competitively blocks iodide from entering the thyroid gland, many of the adverse effects of perchlorate exposure in the low dose range are similar to those of iodine deficiency. The nature and severity of the effects are related to the extent of exposure and the iodine status of the individual.

As discussed in the previous section, pregnant women and their fetuses are considered sensitive subpopulations, especially those who are not getting the required amount of iodine. OEHHA also identified three additional sensitive subpopulations, (i) lactating women, especially those who are getting less than the sufficient amount of iodine, (ii) infants, and (iii) individuals with thyroid problems.

Lactating mothers are considered a sensitive subpopulation because their need of iodine is greater and thus they are more at risk of getting an insufficient amount of iodine from the diet. NAS (2001) suggests an Estimated Average Requirement and a Recommended Dietary Allowance of iodine of 209 μg/day and 290 μg/day, respectively, for lactating mothers. These levels are almost two-fold higher than the Estimated Average Requirement of 95 μg/day and the Recommended Dietary Allowance of 150 μg/day determined for adults (age 19 years and older).

At sufficiently high doses, perchlorate can inhibit the NIS in the mammary gland and reduce the secretion of iodide into the breast milk. Since breast milk is the sole source of iodine for some infants and iodine is necessary for normal brain development, an adequate level of iodine in breast milk is vital to the well-being of breast-fed infants. Laurberg *et al.* (2004) reported that smoking by nursing mothers was associated with a reduction in iodine in breast milk and a decrease in urinary iodine in neonates. Tobacco smoke is known to contain thiocyanate, which is also a NIS inhibitor.

Perchlorate has been detected in human breast milk, showing that breast milk is a viable exposure pathway. There is information indicating that neonates are less capable of maintaining normal thyroid hormone production by using iodide stored in the thyroid, if there is a reduction in thyroidal iodide uptake. Van de Hove *et al.* (1999) demonstrated that newborns have less thyroid hormone stored in the thyroid gland and the turnover rates of the intrathyroidal pool of T4 in the preterm and term newborns are much higher than that of adults.

Finally, individuals with thyroid problems or impaired thyroid functions are also believed to be more sensitive to the anti-thyroid effects of perchlorate.

The following equation was used to estimate health-protective water concentrations (C, in mg/L) for pregnant women:

$$C = \frac{BMDL \times RSC \times (BW/WC)}{UF}$$

$$= \frac{0.0037 \text{ mg/kg-day} \times 0.6 \times (25.2 \text{ kg-day/L})}{10}$$

$$= 0.0056 \text{ mg/L (rounded to 0.006 ppm, or 6 ppb)}$$

where:

BMDL = the lower limit of a one-sided 95 percent confidence interval of a perchlorate dose that reduces mean thyroidal iodide uptake by five percent;

RSC = relative source contribution; a value of 60 percent is used for pregnant women to account for exposure to perchlorate in food such as farm produce and cow's milk;

(BW/WC) = the ratio of body weight (kg) and tap water consumption rate (L/day); the ratio for the 95th percentile of the pregnant woman population is estimated to be 0.0252 kg-day/mL or 25.2 kg-day/L (OEHHA, 2000); and

UF = an uncertainty factor of 10 is used to account for interindividual variability.

The uncertainty factor of 10 for interindividual variability accounts for population variability not captured by the Greer *et al.* (2002) study. There were only 37 healthy adults in the Greer *et al.* study and the variability of the study data is likely to be smaller than that in the general population. Furthermore, the study population did not include individuals with low iodine intake, pregnant women, or infants who could be more sensitive to perchlorate. There are also PBPK modeling results showing that the rat fetal thyroid is more sensitive to the inhibitory effect on thyroidal iodide uptake of perchlorate than the male adult rat, pregnant rat, lactating rat, and the neonatal rat (Clewell *et al.*, 2003).

It has been suggested that an additional uncertainty factor of three be applied to account for the short duration of the Greer *et al.* (2002) study. There is some evidence that iodine uptake is inhibited very quickly after exposure begins and the inhibition does not worsen as exposure continues. Furthermore, it can be argued that conceptually, if there is no reduction in thyroidal iodide uptake, there is no reduction in stored iodide, and extending the exposure duration is not likely to have an impact on the thyroid function. For this reason, no additional factor is judged to be necessary to account for the short duration of the critical study, and an overall uncertainty factor of 10 is used for estimating a health–protective water concentration.

It should be noted that in addition to the use of an uncertainty factor of 10, OEHHA has made a number of decisions to ensure the derived water concentration is health protective. For instance, the identification of the point of departure, prevention of thyroidal iodide uptake, is a health-protective decision since it is intended to prevent the very first step of a process that leads to thyroid hormone imbalance and other related adverse health effects. OEHHA uses a BMD_{05} (rather than a BMD_{10} or a higher response rate) and a BMDL (i.e., the lower 95 confidence level of the BMD) as the point of departure in the benchmark dose modeling. The choice of using the 95th percentile of the water consumption rate and body weight ratio of pregnant women is also health-protective.

Recent food analyses (Smith and Jackson, 2003; Kirk *et al.*, 2003) detected perchlorate in lettuce, cucumbers, strawberries, dairy milk, and human breast milk. Though the available data do not allow detailed quantitative analysis, they do provide a reason for concern that consumption of contaminated food may increase the overall exposure to perchlorate. In addition, normal thyroid function can be affected under the following situations:

- Some vegetarian diets may have low iodide content (Remer *et al.*, 1999); goitrogens are found in certain food such as millet, kelp, maize, bamboo shoots, sweet potatoes, lima beans, cabbages, turnips, and mustard.
- Exposure to environmental contaminants which affect thyroid function, such as nitrate (Van Maanen *et al.*, 1994), polychlorinated biphenyls and dioxins (Porterfield, 1994 and 2000; Bastomsky, 1976).
- Selenium deficiency is believed to be linked to hypothyroidism (Pizzulli and Ranjbar, 2000; Lee *et al.*, 1999).
- Smoking was found to be associated with thyroid volume and goiter prevalence in areas with iodine deficiency (Knudsen *et al.*, 2002). Tobacco smoke contains goitrogens (e.g., thiocyanate).

Because of the detection of perchlorate in produce samples and the existence of other goitrogens in the environment, an RSC of 0.6, or 60 percent, is assumed in the development of the PHG.

There are concerns about nitrate in food. Nitrate is an NIS inhibitor and in sufficiently high doses it may act synergistically with perchlorate. There is a human study indicating that at a normal nitrate ingestion rate, nitrate is not likely to have a significant impact on the thyroidal uptake of iodine. Lambers *et al.* (2000) administered a daily oral dose of 15 mg sodium nitrate per kg body weight (approximately three times the allowed daily intake) for 28 days to ten human volunteers. At the end of the exposure period, there was no change in the thyroidal iodide uptake of the volunteers. Both the control group and the exposed group were on an iodine-restricted and low-nitrate diet. The researchers also reported that the treatment had no effect on the serum T4, T3, and TSH levels. This value of 15 mg sodium nitrate per kg body weight is more than 2,000-fold greater than the lowest perchlorate dose tested, 0.007 mg/kg body weight, in the Greer *et al.* study. OEHHA has previously developed a PHG for nitrate (OEHHA, 1997). If such issues suggest new concerns for nitrate exposure, they will be considered in the next review of the nitrate PHG.

For comparison purposes, health-protective concentrations of perchlorate for lactating women, infants, and adults are provided in Table 29. Consistent with the estimation of a health-protective concentration for pregnant women, an RSC of 60 percent and an overall uncertainty factor of 10 are applied for the lactating woman and adult. For the infant, a

RSC of 100 percent is used because it is assumed that milk is the only food source for the infant. A smaller uncertainty factor of three is used for the infant. This is because traditionally, an uncertainty factor of 10 is used to account for interindividual variability, which is assumed to include a factor of approximately three (or half a log unit) for differences in toxicokinetics and another three for differences in toxicodynamics. In the case of infant exposure estimation, an infant specific BW/WC ratio was used, which accounted for up to a 6-fold difference in toxicokinetics between infants and adults. It should be noted that the differences in toxicokinetics between infants and adults might have been over-estimated. Using PBPK modeling, U.S. EPA (2002) concluded that uptake and elimination kinetics of perchlorate are such that the resultant time-integrated perchlorate concentrations in blood (area under the curve) for adults (70 kg) and children (15 kg) should be about the same. Due to these considerations, a full interindividual variability factor of 10 for infants did not appear warranted.

Table 29. Estimated Health-Protective Water Concentration for Various Subpopulations

Target sub-population	BW/WC (kg-day/L) *	RSC	UF	Health-protective concentration (mg/L or ppm)
Pregnant woman and her fetus	25.2	0.6	10	0.0056
Lactating woman	26.7	0.6	10	0.0059
Infant	5.99	1.0	3	0.0074
Adult	35	0.6	10	0.0078

* BW/WC values are obtained from "Technical Support Document for Exposure Assessment and Stochastic Analysis" (OEHHA, 2000) except for adult, which is calculated using the default values of 70 kg for body weight and 2 L/day for water consumption.

Based on the methods and assumptions described above, OEHHA establishes a PHG of 6 ppb (μg/L), a level that is health-protective for lifetime exposure to perchlorate in drinking water, and is also protective of sensitive subpopulations including pregnant and lactating women, fetuses, and infants.

Carcinogenic Effects

Serum thyroid and pituitary hormones of rodents are highly sensitive to perchlorate exposure. When exposed to perchlorate in drinking water for 14 or 90 days, serum T3, T4 and TSH levels were significantly changed at doses as low as 0.01 mg/kg-day (Springborn Laboratories, 1998). In contrast, human adults that are not iodide deficient appear to be less sensitive to the perturbation of thyroid hormone homeostasis by a 14-day exposure to perchlorate. Greer *et al.* (2002) and Lawrence *et al.* (2000) showed that human T3, T4, and TSH levels were not affected by short-term perchlorate exposure

(1-2 weeks) at doses as high as 0.14 mg/kg-day. Brabant *et al.* (1992) pretreated a group of male volunteers with iodine (200 μg/day) for 4 weeks and followed with an oral daily perchlorate dose of 13 mg/kg-day for another 4 weeks. At the end of the study, they found the subjects' serum T3 and T4 levels were not changed, although the serum free T4 levels were significantly depressed. The serum TSH levels were not elevated. Based on these data, it appears that human adults are not as sensitive as rodents to the perturbation of thyroid hormones caused by perchlorate that may ultimately lead to thyroid tumors.

Furthermore, there are difficulties in estimating cancer potency of perchlorate based on animal cancer data because of differences in iodine deficiency and thyroid disease status (background rates) in control animals and the human population. For the reasons described, a quantitative dose-response evaluation is not performed for the carcinogenic effects of perchlorate. It is reasoned that by setting the perchlorate PHG low enough to avoid impacts on thyroid iodine status, all other potential adverse thyroid effects, including benign and malignant thyroid tumors, will be prevented.

RISK CHARACTERIZATION

Perchlorate salts have been widely used as an oxidizer in solid propellants for rockets and missiles since the mid-1940s. Because of its finite shelf life, perchlorate must be periodically replaced. As a consequence of this use, large volumes of perchlorate have been disposed of since the 1950s and some of them have found their way into soil and aquifers that are needed as drinking water sources. Perchlorate is highly mobile in aqueous systems and can persist for many decades under typical groundwater and surface water conditions. As of February 2004, perchlorate detections have been reported in 348 drinking water sources in California. They are primarily groundwater wells, although sources containing water from the Colorado River have also been contaminated (DHS, 2004b).

As there is no existing drinking water regulation for perchlorate, DHS (2000) established an action level of 18 μg/L (ppb) for perchlorate. In early 2002, based on a draft risk assessment on perchlorate released by U.S. EPA (2002) and the detection limit that can be generally achieved, DHS (2004a) reduced the action level to 4 μg/L (ppb). The Califorina State drinking water action level is now being changed to 6 ppb.

Data from human studies indicate that an oral dose of perchlorate is almost completely absorbed from the gastrointestinal tract and is excreted primarily unchanged via the urine. In an occupational study where the urinary perchlorate levels of two workers during and after work shifts were monitored, it was found that the elimination of perchlorate appears to follow a first-order kinetic pattern with an elimination half-life of 8 hours.

Potassium perchlorate has been used to treat Graves' disease in humans, and most of the high-dose toxicity data on humans are obtained from clinical studies. At the 10-20 mg/kg-day range, some patients after being administered with perchlorate for several weeks reported gastrointestinal irritation, skin rash, and nausea. In a few occasions, agranulocytosis and aplastic anemia have also been reported.

Perchlorate is known to compete with iodide for a transport protein called NIS. NIS can be found in salivary gland, stomach, lactating mammary gland, and thyroid tissues. In several animal as well as human studies (Yu *et al.*, 2000; Lawrence *et al.*, 2000; 2001; Greer *et al.* 2002), perchlorate even at relatively low doses has been shown to significantly reduce or inhibit thyroidal iodide uptake in acute and sub-chronic exposures. Since iodide is a key ingredient of thyroid hormones and perchlorate inhibits iodide absorption by the thyroid, depending on dosage, perchlorate can reduce the production of thyroid hormones and disrupt thyroid-pituitary homeostasis.

This has been confirmed in animal studies. At relatively low doses (0.01-0.1 mg/kg-day) perchlorate exposure causes depression of serum thyroid hormones (T3 and T4) and elevation of serum TSH. At higher doses (3-30 mg/kg-day), perchlorate induces thyroid follicular cell hypertrophy, thyroid follicular cell hyperplasia, or thyroid adenoma in the exposed animals. In several developmental studies, perchlorate exposure was found to be associated with a decrease in thyroid gland follicular lumen size, depression in serum T3 and T4 levels, elevation in serum TSH, and motor activity changes in rat pups (U.S. EPA, 2002). In a neurodevelopmental study (Argus Research Laboratories, Inc., 2001), morphometric changes were noted in several brain regions of pups exposed to perchlorate in utero and after birth. These changes are significant even at the lowest ammonium perchlorate dose tested of 0.01 mg/kg-day (or 0.0085 mg/kg-day, based on perchlorate anion alone). However, the dose-response relationships of the brain morphometric measurements are not monotonic, they resemble either an inverted U or U-shape curve (U.S. EPA, 2002).

The sensitivity of human and rodent thyroidal NIS towards the inhibitory effect of perchlorate appears to be similar. In an injection study reported by Yu *et al.* (2000), inhibition of thyroidal iodide uptake was observed in male rats at doses as low as 0.1 mg/kg. In several drinking water studies, human volunteers exposed to perchlorate in the 0.02 to 0.14 mg/kg-day range for up to 14 days showed reduced thyroidal iodide uptake.

However, there are short-term exposure data to indicate adult humans that are not iodide deficient are better than rodents in maintaining serum T3, T4 levels when exposed to perchlorate. For instance, human volunteers exposed to perchlorate in drinking water at targeted doses between 0.14 and 0.5 mg/kg-day for 7 or 14 days showed no significant changes in serum T3, T4, and TSH (Lawrence *et al.*, 2000; Greer *et al.*, 2002). Even at doses as high as 12 mg/kg-day (4-week exposure), human volunteers showed no significant changes in serum T3 and T4 levels. Serum TSH levels were depressed and intrathyroidal iodine concentrations were reduced in the volunteers. When human volunteers were dosed at 12 mg/kg-day for more than 4 weeks, thyroid enlargement was observed (Brabant *et al.*, 1994, as cited in U.S. EPA, 2002). By contrast, several 14-day drinking water studies showed depression in serum T3, T4, and elevation in serum TSH in rodents exposed to doses as low as 0.01 or 0.1 mg/kg-day (Caldwell *et al.*, 1995; Springborn Laboratories, 1998; Keil *et al.*, 1998; Yu *et al.*, 2000). This conclusion is weakened by the high dietary iodide intake of the volunteers tested, and in light of the findings of decreased serum T4 in newborns with parental exposure to low levels of perchlorate in drinking water (Schwartz, 2001).

Ammonium perchlorate was tested in a battery of genotoxicity tests, and found to be negative in all tests (U.S. EPA, 1998a, 2002). This is consistent with the fact that perchlorate is relatively inert at physiological conditions and does not appear to be metabolized to mutagenic or clastogenic metabolites in humans as well as test animals.

There are limited carcinogenic data on perchlorate in humans. Two ecological studies did not find an association between increased cancer risks and exposure to perchlorate in drinking water.

Carcinogenicity data in animals are also limited. In a two-generation reproductive toxicity study (Argus Research Laboratories, 1999), thyroid follicular cell adenomas were observed in two male Sprague-Dawley rats (2/30) exposed to 30 mg/kg-day ammonium perchlorate in utero and after birth. No such tumors were found in the vehicle control (0/30). Though the incidence is not significant by using standard tests (e.g., Fisher's exact test), the fact that the tumors were found in 19-week old rats and the historical incidence of this type of tumor in male Sprague-Dawley rats in 2-year studies reported in the literature is only 3-4 percent make the finding significant (U.S. EPA, 2002).

The PHG of 6 ppb is derived from a human drinking water study reported by Greer *et al.* (2002). Using the benchmark dose method, a BMDL of 0.0037 mg/kg-day was identified. The value represents the lower limit of a one-sided 95 percent confidence interval of a perchlorate dose that reduces mean thyroidal iodide uptake by five percent. A health-protective drinking water level was estimated by using an overall uncertainty factor of 10, assuming a body weight to tap water consumption rate ratio of 25.2 kg-day/L for pregnant women (OEHHA, 2000), and a relative source contribution of 60 percent.

The uncertainty factor of 10 is used to account for interindividual variability because the subject population in the Greer *et al.* (2002) study is not the same as the general population. The subject population did not include pregnant women, infants, and individuals with iodine deficiency or marginal iodine deficiency. The sensitivity of thyroid gland of fetuses and infants towards the inhibitory effect of perchlorate may be higher than that observed in adults. As iodide and perchlorate compete for the same protein receptor (NIS), the relatively high iodine intakes of the subjects might have lowered the sensitivity of the thyroid towards the inhibitory effects of perchlorate. Dietary iodine intake and thyroidal iodide uptake are known to vary among individuals; they are affected by the type of food one eats (some food is rich in iodine while others contain goitrogens), smoking habits (tobacco smoke contains goitrogens), and exposure to environmental contaminants (such as nitrate, polychlorinated biphenyls and dioxins). The interindividual variability of the general population is likely to be greater than that in the study.

The Relative Source Contribution (RSC) is the proportion of the total daily exposure to perchlorate that is to be allocated to drinking water. If no other sources of the contaminant are known, then U.S. EPA recommends a value of 80 percent be allocated to drinking water. If there are other detectable but unquantifiable sources, U.S. EPA suggests a value between 20 and 50 percent of the total daily exposure be allocated to drinking water. Finally, if data exist to estimate contributions from other sources, that data can be used to calculate the source contribution.

Preliminary results have demonstrated the presence of perchlorate in some food (Kirk *et al.*, 2003; Smith and Jackson, 2003). A low level of perchlorate has also been detected in a single sample of human breast milk. While a precise value for the RSC cannot be established at this time, current scientific evidence suggests that the estimated exposure to perchlorate in water is greater than from other sources. For this reason, the RSC for this PHG is set at a level of 60 percent (instead of 20-50 percent) because OEHHA believes that the daily exposure to perchlorate would be predominantly from contaminated drinking water, not from other sources, e.g., food. Studies are underway to quantify perchlorate levels in various food types. DHS has indicated that based on a review of current research data, there is no imminent health threat from perchlorate in food that would require a change in diet.

Four sensitive subpopulations are identified in this evaluation: (i) pregnant women and their fetuses, especially those who are getting less than a sufficient amount of iodine; (ii) lactating women, especially those who are getting less than a sufficient amount of iodine, (iii) infants, and (iv) individuals with thyroid problems.

A number of human studies have shown that pregnancy stresses the thyroid (Crooks *et al.*, 1967; Glinoer *et al.*, 1990, 1992, 1995; Smyth *et al.*, 1997; Caron *et al.*, 1997; Brent, 1999; Kung *et al.*, 2000). In areas of iodine deficiency (intake level <100 μg/day), there is an increased risk of abnormally low serum triiodothyronine (T3) and thyroxine (T4) levels, thyroid enlargement as well as goiter in pregnant women. The nature and severity of changes in thyroid and thyroid function are related to the severity of iodine deficiency. In three prospective studies (Romano *et al.*, 1991; Pedersen *et al.*, 1993; Glinoer *et al.*, 1995), it was shown that the pregnancy-related thyroid enlargement could be prevented by administering iodide salts to the pregnant women. These results confirm that iodine deficiency is the main causative factor of thyroid enlargement during pregnancy.

Urinary iodine concentrations are often used as an indicator of the adequacy of iodide intake of a population. According to the NHANES III data, the median of the population was 14.5 μg/dL and 11.7 percent of the population was found to have low urinary iodine concentrations (<5 μg/dL) (Hollowell *et al.*, 1998). The median urinary iodine concentrations in iodine-sufficient populations should be greater than 10 μg/dL, and no more than 20 percent of the population should have urinary iodine concentration less than 5 μg/dL. If one applies this definition, there appears to be no iodine deficiency in the general population. However, the data do not preclude the possibility that some women of childbearing age are not getting the sufficient daily amount of iodide.

More significantly, developing fetuses and neonates are considered particularly sensitive to iodine deficiency. It is because of the irreversible changes that can occur during this period of rapid structural and behavioral development. Severe iodine deficiency (<25 μg/day) during pregnancy can cause prenatal death and cretinism (WHO, 1994; as cited in Hollowell *et al.*, 1998). Cretinism is characterized by mental deficiency, deaf mutism and spastic diplegia[8]. Even less than severe iodine deficiency during pregnancy has been linked to adverse neuropsychological development and a reduction of intelligence quotient (IQ) of the child (Vermiglio *et al.*, 1990; Bleichrodt and Born, 1994). Studies indicate that hypothyroidism or small decrements in maternal free T4 within what is generally considered the "normal" range (lowest 10 percent) during the

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[8] Bilateral paralysis of both sides of any part of the body.

first trimester are associated with impaired neuropsychological development in the child (Pop *et al.*, 1999; Pop *et al.*, 2003; Haddow *et al.*, 1999; Klein *et al.*, 2001).

Adverse effects of perchlorate exposure on the development of fetal brain have also been observed in rats. In a study reported by Argus Research Laboratories (2001), ammonium perchlorate in water was administered to female rats throughout the gestation period at target doses of 0, 0.01, 0.1, 1 or 30 mg/kg-day. Several brain areas (e.g., corpus callosum) in the treated male and female pups varied significantly from controls in size. The design of the study and the way pups' brain were sectioned had been criticized. Interpretation of the study is also made difficult due to the unusual dose-response relationships of the brain morphometry data.

NIS is known to be present in the placenta and lactating mammary glands. At sufficiently high doses, perchlorate can impact the NIS in these tissues and reduce the iodine supply to fetuses and breast-fed infants. Since breast milk is the sole source of iodine for some infants and iodine is necessary for normal thyroid function and brain development, adequate level of iodine in breast milk is vital to the well-being of breast-fed infants. Furthermore, if there were a reduction in thyroidal iodide uptake, neonates are less capable to maintain normal thyroid hormone production by using the iodide stored in the thyroid. Van de Hove *et al.* (1999) demonstrated that newborns have less thyroid hormone stored in the thyroid gland and the turnover rate of the intrathyroidal pool of thyroid hormones in newborns is much higher than that of adults.

Individuals with hypothyrodism have impaired thyroid function; a significant reduction in thyroidal iodide uptake may exacerbate the illness. For this reason, they are also identified as a sensitive subpopulation.

The human data presented in the section on hematological effects suggest that humans may be more sensitive to these effects than animals thus far studied. However, it is important to note that these data were mostly derived from clinical studies, where high doses were used (6-14 mg/kg-day). Compared with the identified BMDL of 0.0037 mg/kg-day based on the prevention of inhibition of iodide uptake into the thyroid, an oral effective dose of 6 mg/kg-day is approximately 1,500 times higher. It is believed that a PHG of 6 ppb is adequate to protect against the known high-dose hematological effects of perchlorate.

OTHER REGULATORY STANDARDS

Currently, there is no Federal or California MCL for perchlorate. The current California State action level is 4 ppb (DHS, 2004a), now being changed to 6 ppb. Several other states have action levels in the range of 1-20 ppb as shown in the table below

State and Tribal Advisory Levels for Perchlorate (U.S. EPA, 2003; DHS, personal communication)

California	6 ppb
New York	5 ppb and 18 ppb
Texas	4 ppb, 7 ppb or 10 ppb
Arizona	14 ppb
Massachusetts	1 ppb
Maryland	1 ppb
New Mexico	1 ppb
Nevada	18 ppb

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